Describing final diagnosis and outcome for patients investigated for suspected acute coronary syndrome at a regional, public South African emergency centre.

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Declaration

By submitting this dissertation electronically, I, Diulu Kabongo declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Signature: **Date: December 2018**

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Abbreviations

ACS: Acute coronary syndrome

CK: Creatine kinase

CV: Coefficient of variation

EC: Emergency centre

ECG: Electrocardiogram

GRACE: Global Registry of Acute Coronary Events

HIC: High-income country

HIV/AIDS: Human immune-deficiency virus/Acquired immune-deficiency syndrome

LDH: Lactate dehydrogenase

LMIC: Low- to middle-income country

ng/L: Nanogram per litre

NCD: Non-communicable diseases

NSTEACS: Non-ST elevation acute coronary syndrome

NSTEMI: Non-ST elevation myocardial infarction

OR: Odds ratio

SA: South Africa

SBP: Systolic blood pressure

SD: Standard deviation

STEMI: ST elevation myocardial infarction

TIMI: Thrombolysis in Myocardial Infarction

USA: United States of America

PART A: LITERATURE REVIEW

PART A: LITERATURE REVIEW

Objectives of the literature review

- To briefly describe the trends for the global, sub-Saharan African, and South African burden of cardiovascular disease
- To briefly describe the prevalence of acute coronary syndrome globally, in sub-Saharan Africa, and South Africa
- To briefly review the various cardiac markers available for the diagnosis of acute coronary syndrome

Literature search strategies, inclusion and exclusion criteria

Searches were conducted to include relevant articles dated 2009 and later. Given a paucity of data, earlier publications were accepted for information related to Africa. Search engines used included: Pubmed/ Medline and Google Scholar. The following keywords were used: burden, ischaemic/ ischaemic, cardiovascular, Africa, Acute coronary syndrome, myocardial infarct, STEMI, NSTEMI, management, unstable angina, troponin, cardiac markers. The following phrases were also used during the Google Scholar search: Burden of cardiovascular diseases; Ischaemic heart disease in Africa; Acute coronary syndrome-global perspectives; Acute coronary syndrome in Africa; Definition of myocardial infarct; Management of non-ST elevation acute coronary syndrome; Unstable angina pectoris and more sensitive troponin assay; History of cardiac markers and diagnosis of acute coronary syndrome; Elevated troponin T in non-coronary diseases; Troponin T and non-coronary diseases; Cardiac markers; Interpretation of cardiac markers.

Titles and abstracts were initially screened for relevance to the review and those deemed to have low relevance or poor external validity were excluded. Full-text copies of selected articles were extracted that fulfilled the inclusion criteria below. The reference sections of full-text papers were then evaluated further for papers not found through the initial search. Abstracts of these papers were then considered as well, and the process repeated until no more papers were found.

High-quality evidence, including systematic reviews, was sought to address the aim and objectives. Papers were appraised against the relevant checklist from the Oxford Centre for Evidence-Based Medicine. (http://www.cebm.net/critical-appraisal/). A representation in tabular form of appraised papers is not required for the MMed and therefore was omitted. Very little data were available that directly addressed some parts of the aim and objectives – particularly with regards to literature related to the African context – and thus criteria were applied less stringently here.

Inclusion criteria:

- Human studies
- English language
- Access to full text through institutional library
- Date of publication: 2009 and later

Introduction

A global burden of cardiovascular disease

The global burden of disease is shifting from communicable to non-communicable diseases (NCD) (1-3). Without an appropriate response to the spiralling epidemic, cardiovascular diseases and stroke will become the commonest causes of death and disability among NCDs by 2020 (1). The annual global death due to cardiovascular diseases will surpass HIV/AIDS by 2030 at the current rate of growth (4). Ischaemic heart diseases contributes most to cardiovascular disease-related mortality and disability-adjusted life years worldwide (3, 5, 6). Currently, more than 80% of cardiovascular related deaths occur in low- to middle-income countries (LMICs) (1, 6, 7).

In LMICs, the increase of ischaemic heart diseases is driven by transformational economic and lifestyle changes (6, 8, 9). Risk factors for ischaemic heart disease includes: hypertension, raised serum cholesterol level, cigarette smoking, diabetes mellitus, poor physical activities and a high fat diet (7, 10, 11, 12, 13). Globally, these risk factors are similar according to the INTERHEART study (10). In many LMICs, ischaemic heart disease risk factors have been increasing over time. Brazil, for instance, tripled their ischaemic heart disease risk factors from 4.1% to 13.9% between 1975 and 1997 (6). Systolic blood pressure (SBP) has increased in sub-Saharan Africa whilst decreasing in high income countries (HICs) (6). Consumption of sugary beverages, processed food and alcohol have been increasing dangerously matched with low level physical activity in both LMICs and HICs (6). Cardiovascular diseases, type 2 diabetes mellitus, cancer, chronic lung diseases and depression are the major NCDs in South Africa (SA) (8). When counting disability-adjusted life years, the World Health Organisation estimated that 28% of the burden of disease in SA was due to NCD in 2004, i.e. two to three times higher than in developed countries (8). Unfortunately, prevention of NCDs is overlooked as disproportionate attention is paid to higher prevalence burdens of HIV/AIDS and tuberculosis (12).

The ACCESS (Acute Coronary Events- a Multinational Survey of Current Management Strategies) study found levels of initial care for acute of coronary syndrome (ACS) in SA, particularly in private hospitals, similar to HICs (4). Disappointingly, continuation of medications and lifestyle modifications were poor (10). Indeed, only 38% of patients quit smoking in SA compared to 42% in HICs (10). This attempt to understand the epidemiology of ACS in sub-Saharan Africa is commendable as studies are lacking in this area (9, 13).

In a nutshell, aggressive treatment and prevention of ischaemic heart diseases are yielding positive results in HICs (6). Conversely, limited access to adequate diagnostic and therapeutic options during and after an episode of ischaemic heart disease fuel particularly early-age death in LMICs (7, 12, 14). The same applies in South Africa where poorer communities in urban areas are more affected by NCDs (8). Indeed, the poorer regions of Cape Town have shown higher mortality secondary to NCDs compared to the more affluent regions in the south and north of the city (8).

Acute coronary syndrome

The approach to ACS diagnosis, besides the clinical examination and the electrocardiogram, involves the use of highly specific cardiac troponins for diagnosis and risk stratification (10, 15, 16). Assays use monoclonal antibodies to specifically detect either the cardiac troponin T or I (17- 19). Rising troponin levels are more specifically linked to cardiac necrosis, but elevated troponin levels may also be found in non-ACS conditions like heart failure, cardiomypathies, myocarditis, renal failure, tachyarrhythmias, pulmonary embolism, and strenuous exercises (17, 18, 20, 21). Current epidemiological knowledge about ACS relates overwhelmingly to studies performed in HICs (6). In the United States of America (USA), six million people are investigated annually for suspected ACS, among whom approximately a tenth are hospitalised with a confirmed diagnosis of ACS (19). In contrast to ACS patients from LMICs who tend to die younger, ACS patients from the USA live up to a median age of 68 years (5, 14, 22). Arguably, younger deaths resulting from ACS not only affects economic productivity, but also economic security for entire families.

Sub-Saharan Africa's rising ischaemic heart disease burden necessitates a holistic approach to focus not only on infectious diseases as was done in the past, but also on NCDs (8, 19). Much can be gained from local research to improve our understanding of cardiovascular disease. The study presented in part B is a small but significant study that contributes to the understanding of local trends in acute presentation, testing and outcomes of patients presenting with suspected ACS at a single public hospital. We hope that the findings of this study can aid local policy guidelines and collectively, with similar research, improve the acute care and outcome of patients suffering from ACS in South Africa.

Definition of acute coronary syndrome

Acute coronary syndrome represents a spectrum of clinical entities related to acute myocardial ischaemia (16). Based on the findings of a 12-lead electrocardiogram (ECG), ACS is grouped as follows (16, 22):

- Acute ST elevation myocardial infarction (STEMI) that presents with new ST-segment elevation on the ECG.

- Non-ST elevation ACS (NSTEACS) that presents with new ST-segment depression, T wave changes, or no ECG abnormalities. NSTEACS comprises of the unstable angina and non-ST elevation myocardial infarction (NSTEMI).

Unlike unstable angina, NSTEMI is a severe form of ischaemia resulting in myocardial damage and a subsequent release of biomarkers of myocardial injury (22). A release of biomarkers is not found with unstable angina (22). Furthermore, to avoid the different diagnoses associated to cardiac biomarkers release detected by ever sensitive laboratory tests, the third definition of acute myocardial infarction emphases the detection of a rise and/or fall of cardiac marker values together with other criteria to reach the diagnosis of acute myocardial infarction (16).

Pathogenesis and pathophysiology of acute coronary syndrome

Acute coronary syndrome has a heterogeneous aetiology resulting from five principal mechanisms (16, 23): plaque rupture (from atherosclerosis) with acute thrombosis, progressive mechanical obstruction, inflammation, secondary unstable angina due to e.g. severe anaemia, hyperthyroidism, etc., and dynamic obstruction (vasoconstriction). Many of these mechanisms act concurrently, though the commonest mechanism remains atherosclerosis (23). In case of atherosclerosis, a thrombus can partially or completely occlude the coronary vessels, respectively resulting in different clinical presentations (23). Mostly the occlusion tend to be partial (or transient) resulting in myocardial ischaemia, but with no ST-segment elevation (unstable angina or NSTEMI) (23, 24).

Epidemiology of acute coronary syndrome

Worldwide, chest pain is a common cause of hospital admission (25). In Europe and the USA together, about 15-20 million people present to emergency centres (ECs) annually with chest pain (26). Yearly, about 1.4 million ACS patients are admitted into USA hospitals (27). Yet, only about 10% of these end up with a diagnosis of STEMI (28). Acute coronary syndrome remains an important diagnosis in the USA with estimations of an episode of ACS every 25 seconds and an ACS-related death every minute (27). Advances in acute care in high income regions has reduced complications of ACS by 50% (27)). In the United Kingdom, sustained preventive measures have dropped ACS incidence by 30% (29).

Acute coronary syndrome has been steadily increasing in Africa. Earlier studies by Florentin revealed no evidence of myocardial infarction during autopsies in Uganda in 1963 (30). Similarly, referring to a study by Shaper, there was no evidence of myocardial infarction using clinical and laboratory criteria in Kenya in 1962 (30). Conversely, 2007 data from Senegal show an ACS incidence of 6.8% and rising (31). These changes reflect an epidemiological transition likely due to lifestyle

modifications (30).Showing no end to this debate Ntsekhe highlighted uncertainty about the contribution of ischaemic heart diseases to the burden of cardiovascular diseases in Africa in 2013 (4). It is fair to say that ACS management lags behind in Africa; despite the ACCESS study showing initial quality of care in private hospitals in South Africa, similar to worldwide performance (10, 12). Private care in South Africa makes up a small proportion of healthcare delivery in South Africa. Perhaps this point is more poignantly demonstrated in Kenya, where a 2014 study revealed that less than 50% of STEMI patients received thrombolysis when indicated (32).

The response to what appears to be a rising demand locally in ACS care has been fairly underwhelming. From the patchy literature available it appears that there are many small areas of excellence mixed with many more areas of less than excellence. This is unhelpful in a setting where patients have little choice regarding their healthcare options. We believe that more needs to be done to describe the local acute burden.

Diagnosis of acute coronary syndrome

General approach

When left untreated, patients with ACS have a high risk for further cardiac complications (24, 28). These complications include: pulmonary oedema, rupture of the papillary muscles, rupture of the left ventricular free wall or the ventricular septum (23). For this reason, patients with ACS should be identified quickly for prompt management (23). Triage of patients presenting with chest pain should include clinical information (history and symptoms), a 12-lead ECG and biomarker testing (troponin is currently the preferred biomarker). This approach should promptly identify ACS patients and largely avoid the detrimental complications described earlier (10, 13, 33, 34). A strategic use of risk-scoring systems in the consideration of the diagnosis of ACS is beneficial (35). Tools like the Thrombolysis In Myocardial Infarction (TIMI), the HEART (History, ECG, Age, Risk factors, Troponin) score and the Global Registry of Acute Coronary Events (GRACE) scores are well known (35).

Only up to a quarter of patients suspected of suffering with ACS have a confirmed myocardial infarction; effective triage is therefore necessary to not only avoid inadvertent discharge of ACS patients but also unnecessary admissions that may lead to unnecessary investigations (33). Use of biomarkers, particularly those with a high sensitivity in diagnosing myocardial injury, is helping to close this gap (33). Unsurprisingly, the Thrombolysis in Myocardial Infarction-3 study showed that 25% of unstable angina patients diagnosed using CK-MB, turned out to have a positive troponin assay, making unstable angina an uncommon diagnosis (36, 37). This is a notable point, as compared to unstable angina, NSTEMI is associated with an increased risk of mortality and adverse cardiac outcomes (20). An ideal biomarker should therefore be highly sensitive, specific and for which an

assay is simple, inexpensive, reproducible and rapid (20). Also, the use of the delta value as explained below is required in the third definition of acute myocardial infarction (16).

Cardiac biomarkers

During myocardial necrosis, compromise of the cellular membranes' integrity releases a number of biomarkers (38). These include: myoglobin, creatine kinase (CK, particularly its CK-MB isoenzyme); cardiac troponin I, C and T; and lactate dehydrogenase (LDH) (20). Of these biomarkers, only CK-MB and cardiac troponin I and T have been universally used to test for myocardial damage (20, 21). Others are used, but not consistently so. Generally, CK has poor specificity to rule in cardiac muscle damage, as it is also found in great quantities in the skeletal muscles (20). However, CK-MB isoenzyme offers better sensitivity and specificity mainly because only 1-3% of skeletal muscle CK is CK-MB (20, 38). CK-MB is also found in the intestine, diaphragm, uterus and prostate, which affects its accuracy (38). Despite this, CK-MB used to be the biomarker of choice until fairly recently but it has fallen out of favour with the introduction of more sensitive cardiac troponins (20).

Troponins are cardiac and skeletal muscle regulatory proteins whose skeletal and cardiac isoforms are encoded by the same genes (20, 21). However, for troponin I and T, their cardiac and skeletal subforms are different (38). Therefore, cardiac subforms of troponin have high myocardial specificity (18). This high specificity and an ever increasing sensitivity render troponins the biomarkers of choice.

Kinetics of biomarkers (Table 1)

The CK-MB level begins to rise three to four hours after the onset of myocardial necrosis and starts to fall by around 48-72 hours (20, 38). Cardiac troponin levels rise at the same time as CK-MB but fall much later, i.e. four to seven days for troponin I and 10-14 days for troponin T (38).

Table 1: *Cardiac marker levels* (39)

	Onset (hours)	Peak (hours)	Duration
Troponin I	3-12	10-24	3-10 days
Troponin T	3-12	12-48	5-14 days
CK-MB	4-6	24	2-3 days

Interpretations of biomarker results

Manufacturers of laboratory troponin assay kits use different reference ranges for interpretation; these variations reflect differences in standardisation as well as different monoclonal antibodies that affect the sensitivity, specificity and precision of the assays (38). These variations are defined by the

percentile reference limits and the coefficient of variation (CV) (20, 21, 34). The percentile system describes the dispersion of test results among individuals, the upper normal percentile limit is considered to be the 99th percentile and any number greater than the 99th percentile is considered abnormal (38). The CV describes the variation of results obtained on the same assay. The CV determines the precision of the assay (21, 34). Its acceptable cut-off is 10% (20, 41). At present, all troponin T assays are manufactured by one company, whereas troponin I are produced by a number of manufacturers (38). As a result, these troponin I assays differs on the 99th percentile and the CV10% (38).

Over time, manufacturers have rendered assays able to detect increasingly lower levels of troponin (20, 21, 35). Whilst first generation assays had a myocardial infarct cut-off of 500 nanograms per litre (ng/L), most current assays (third generation) use a cut-off of 50 to 100 ng/L (35). Newer assays can detect a troponin leak as low as 3ng/L. The newer assays are termed high sensitivity assays and are able to detect troponin in more than 50% of normal individuals (35, 39). In practice, the ability to detect lower troponin T levels has a greater accuracy at ruling out an infarct early (35). Whilst the third generation assays require sampling at six hours from onset of symptoms (and a repeat sample six hours later), the latest high sensitivity troponin can be performed around three hours from onset of symptoms (also to be repeated at six hours) (20). Unfortunately, with increase in sensitivity, specificity is bound to suffer; specificity was reduced to 80-85% in contrast with earlier generation assays that had a specificity of around 97% (35). Serial testing with a delta value (variation between two consecutive tests) of equal to or more than 20% is therefore required to improve the specificity and rule out false positives (20, 40). Currently, delta testing underpins the interpretation of troponin testing as per the third definition of acute myocardial infarction.(16)

Troponin use in sub-Saharan Africa

Although the literature would suggest that the use of troponin as a diagnostic tool for ACS is commonplace, it is mostly in reference to HICs where that vast majority of related research is also generated. Very little is published about the use of troponin as a test for ACS within the African context. Our search revealed only references to the use of troponin as part of larger studies, but none specifically described its use in any detail. Additionally some anecdotal evidence from South Africa suggests that older generation troponin assays are in use, some that predates the third definition of myocardial infarction. The use of newer generation troponin assays in HICs reduces the market for older ones and instead creates a market for these older (but cheaper) generations of troponin assays in LMICs (communication Dr. Richard Body, 02/12/2016). The problem with using an assay that does not have the accuracy to describe myocardial infarction as per the third definition is that it cannot be used in any algorithm that depends on the third definition. This substantially limits its diagnostic value.

Summary and recommendations

Acute coronary syndrome is a major cause of morbidity and mortality worldwide. It has also become a serious concern in sub-Saharan Africa of late as estimates suggests an upward trend in prevalence. The diagnosis of ACS is underpinned by an appropriate history, an ECG and appropriate testing. Currently troponin testing is considered the gold standard provided it fulfils the criteria as per the third definition of myocardial infarction, but there appears to be anecdotal concern about the use of older generation troponin assays with lower diagnostic accuracy in lower income settings. Specific research is required to better describe the overall demographics and prevalence of ACS in sub-Saharan Africa and its various regions, to describe the quality of care and outcomes locally as compared to internationally, and to describe the validity of earlier generation diagnostic testing among suspected ACS patients locally.

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PART B: MANUSCRIPT IN ARTICLE FORMAT

PART B: MANUSCRIPT IN ARTICLE FORMAT

This manuscript has been formatted for publication in the South African Medical Journal. The guidance for authors can be found in Appendix I.

Title page

Title:

Describing the diagnosis, outcome and prevalence of acute coronary syndrome when investigated with the Roche cardiac reader at a regional, public South African emergency centre

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Abstract

Background

The global burden of disease is shifting from communicable to non-communicable diseases including acute coronary syndrome. There is comparatively less data available regarding acute coronary syndrome in Sub-Saharan Africa compared to elsewhere. Clinical findings, ECG changes and troponin testing forms the mainstay of diagnosis. Many resource limited settings still use dated troponin assays. The aim of this study was to describe the diagnosis, prevalence and outcome of acute coronary syndrome at an urban, public emergency centre in Cape Town, South Africa where an older assay is in use.

Methods

A retrospective, cross-sectional design was used to enrol participants. Comparisons were made between the diagnosis, outcome and troponin result (as per the Roche cardiac reader). Findings were presented as figures and proportions, and associations were tested using the Chi^2-test.

Results

Nine hundred and sixty-nine patients were included, from which 40 (4%) were excluded due to lack of clinical records. Two hundred and fifty-six patients were diagnosed with acute coronary syndrome, from which only 54 were troponin positive ($Chi^2 = 22.1$, $p<0.001$). However, 197 (76.9%) acute coronary syndrome diagnoses turned out to be unstable angina.

Conclusions

Prevalence of ACS was low, with a high proportion of presenting patients indicated as not having disease. However, the prevalence of unstable angina was higher than current trends where more and more sensitive troponin tests are in use. Despite the limitations of the study, assay accuracy should be considered an important variable, striking a balance between patient safety and cost effectiveness. More research is required to explore this further.

Main text of article

Describing the diagnosis, outcome and prevalence of acute coronary syndrome when investigated with the Roche cardiac reader at a regional, public South African emergency centre

Background

The global burden of disease is shifting from communicable to non-communicable disease; without intervention, the morbidity due to cardiovascular diseases will supersede human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) by 2030 (1- 3). Despite a dearth of cardiovascular diseases knowledge in sub-Saharan Africa, more than 80% of cardiovascular-related deaths are estimated to occur in low- to middle-income countries (LMICs) (1- 5). Acute coronary syndrome (ACS) is the commonest cause of death and disability among cardiovascular diseases (3, 5, 6). Aggressive treatment and prevention in high-income countries already yields positive results, hence these treatment reference standards are also considered in LMICs (5). However, the epidemiology, precise patterns and outcomes of ACS management in Africa are poorly documented (2, 7, 8). In LMICs, South Africa included, an increase of ACS appears to be due to transformational economic and lifestyle changes (5, 8, 9). In the INTERHEART study, one of the larger African studies, ischaemic heart disease risk factors were similar worldwide (i.e. hypertension, raised cholesterolaemia, diabetes mellitus, cigarette smoking, poor physical activities and high fat diet) and smaller studies have replicated these findings (4, 7- 11). Moreover, cardiovascular diseases appear to claim younger lives in LMICs, which in turn impacts productivity (4, 10, 12). In contrast, addressing cardiovascular diseases has not matched its growth and solutions remain elusive in LMICs, mainly due to poor availability and/or quality of the resources required for its diagnosis and care (5, 10, 13).

Acute coronary syndrome includes ST-elevation myocardial infarction (STEMI) and non-ST-elevation ACS (NSTE-ACS) (14). The latter comprises unstable angina and non-ST-elevation myocardial infarction (NSTEMI) (14, 15). Besides the clinical and electrocardiogram (ECG) findings, the use of highly sensitive cardiac troponins has become the reference standard for the diagnosis of myocardial infarction, alongside risk stratification for ACS (14- 17). Assays use monoclonal antibodies to specifically detect either the troponin T or I. The accepted reference standard for the upper reference limit of a troponin assay is currently considered at the 99th percentile with a coefficient of variability of less than 10% (14- 16, 18- 20). Importantly, as newer troponin assays continue to become more and more sensitive, and thus able to detect lower and lower levels of biomarker, the diagnosis of unstable angina has become fairly uncommon; perhaps only about 5-10%

of ACS cases (21, 22, 23). Unsurprising, the Thrombolysis in Myocardial Infarction-3 study showed that 25% of unstable angina patients diagnosed using CK-MB, turned out to have a positive troponin assay (22). This is a notable point, as compared to unstable angina, NSTEMI is associated with an increased risk of mortality and adverse cardiac outcomes (18). To counter the reduction of specificity associated with a higher sensitivity, and thus reducing the proportion of false positives, serial troponin assays are also recommended; significant changes of troponin levels usually equal or more than 20% from the baseline over a specified timeframe, implicate myocardial infarction (14, 19, 24, 25).

Although very little is known about the use of troponin testing in LMICs, it is reported anecdotally that due to cost restrictions, many LMIC facilities still make use of older troponin assays that predate current reference standards. The study site is one of those facilities. It is unclear how the use of less sensitive troponin assays with a wider coefficient of variability stack up to an acceptably, safe diagnosis as incorrect interpretation of results could result in unintended harm to patients (13, 17, 24). Therefore, understanding how the diagnostic test for ACS relates to the eventual diagnosis and outcome is an important quality consideration.

The aim of this study was to describe and compare the troponin result, exit diagnosis and outcome (admission, transfer, discharge or death), as well as the prevalence of ACS, in patients in whom ACS was suspected on first assessment at a regional, public emergency centre (EC) where an older assay was being used.

Methods

The study was performed using a retrospective, cross-sectional design. It was conducted at Mitchells Plain Hospital EC, Cape Town, South Africa. The Mitchells Plain catchment area includes a low- to middle-income suburban area within Cape Town. It houses around a third of a million people, mainly of mixed race (91%) (26). About 10% of the Mitchells Plain population has no income and 40.5% have an annual income equivalent to between US$ 2700 and 11000 (26). The EC sees around 3800 patients per month. Although exact figures are unknown, anecdotally, ACS is considered to have an above average prevalence in this area. The hospital does not have a cardiology service or angiography suite, and access to cardiology services, including angiography, is through Groote Schuur Hospital, a tertiary, referral hospital, 23km away. Even so, primary coronary intervention is not consistently available, even at Groote Schuur Hospital.

Study participants were identified via the National Health Laboratory Services as patients who have had troponin T testing performed at the EC over a four-month period between 1st July and 31st October 2015. At Mitchells Plain hospital, all EC medical doctors requests troponin T test upon clinical suspicion of ACS. At Mitchells Plain hospital, clinicians freely use history taking, ECG findings, troponin T testing and any risk scoring tool to reach the diagnosis of ACS. The Study

participants' identification via the laboratory service allowed access to folder numbers and hence tracking of the clinical record. Information obtained from the clinical record included: age, gender, exit diagnosis (ACS/ not ACS on exiting the hospital following either discharge, transfer or death), disposition outcome (discharge from EC, admission to Mitchells Plain Hospital, transfer from hospital to Groote Schuur Hospital or death during admission at Mitchells Plain hospital EC) and documented risk factors (hypercholesterolaemia, hypertension, diabetes mellitus, smoking, positive family history and obesity). The exit diagnosis were taken from the clinical notes as described on death, or discharge or transfer from hospital. The ECG was not specifically evaluated as part of the study protocol. This is further discussed in the limitations section. Exclusions were for missing diagnosis and outcome variables. Patients were not excluded for missing risk factor variables.

The troponin T assay used during the data collection period was the Roche CARDIAC® T Quantitative assay, or Cardiac Reader. This assay has a coefficient of variability greater than 10% at the 99th percentile for the upper reference limit. For the purpose of this study, the troponin T results were dichotomised (positive/ negative) according to local guidance. The test is considered positive if the level is above 100ng/L and negative if below 50ng/L. The assay only provides a range for a troponin T result between 50 and 100ng/L. If this range is reported, a repeat test would usually be performed at six to 12 hours after the first to determine the final result. If the repeat troponin T assay remains between 50 and 100ng/L, the result is considered negative; it is considered positive if it subsequently rises above 100ng/L. Where multiple troponin T tests were performed during a single admission, the first troponin T result, six to 12 hours after symptom onset (or admission in case symptom onset is not described) was used to determine the result. This interpretation mimics the use of the test locally.

A sample size of 384 consecutive subjects meeting the inclusion criteria was required. The sample size calculation assumed a 50% proportion of positive clinical diagnosis (with α=0.05 and β=0.8). Microsoft Excel and SPSS were used for analysis. Numerical data (e.g. age) were expressed as mean and standard deviation (SD). Categorical data (troponin T results, disposition, diagnosis at disposition and risk factors) were expressed as frequencies. To compare troponin T results (positive/negative) to either the disposition diagnosis (ACS/not ACS), or the disposition (survival to discharge from EC, survival to discharge from Mitchells Plain Hospital ward (admission), survival to transfer, and death during admission at Mitchells Plain Hospital EC) the Chi^2-test was used. A p-value of less than 0.05 was considered statistically significant. To compare the disposition diagnosis (ACS/not ACS) to ACS risk factors and troponin result, odds ratios were calculated using univariate logistic regression. Ninety five percent confidence intervals are presented where appropriate as a further measure of precision. The study received ethics approval from the Health Research Ethics Committee at Stellenbosch University (Reference: S16/02/029).

Results

A sample of 969 datasets were collected of which 40 were excluded due to insufficient clinical information. The mean age was 58 years (SD ± 14). There were 420 (45.2%) men included in the sample. Figure 1 provides a summary of the study's main findings. Outcome observations included 911 datasets as 18 patients were discharged after refusing further hospital treatment.

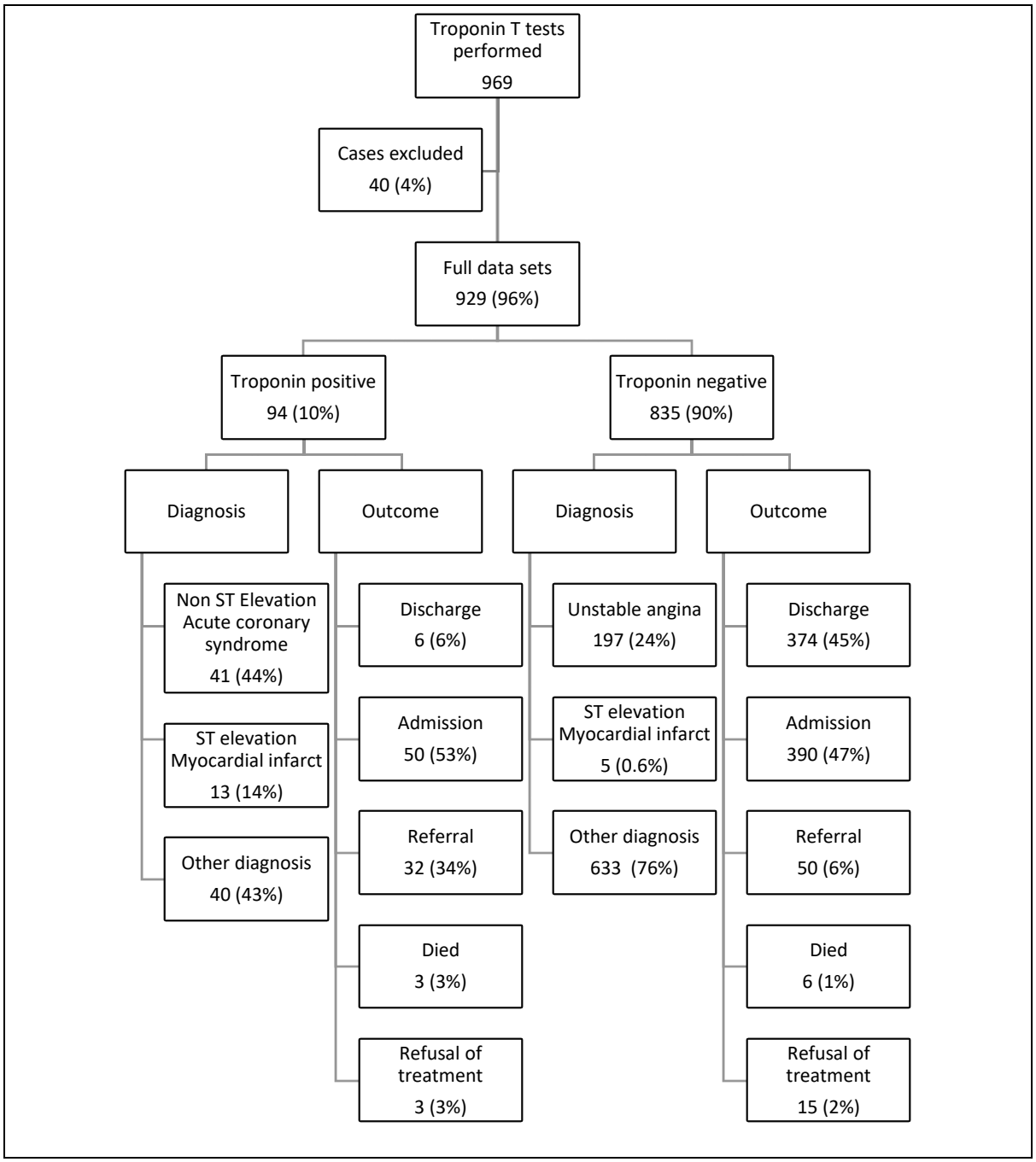

Figure 1: *Summary of study findings*

A diagnosis of ACS was significantly associated with a positive troponin assay when compared to a diagnosis of ACS associated with a negative troponin assay (Chi^2=22.1, p<0.001). Similarly, a

diagnosis other than ACS was significantly associated with a negative troponin assay when compared to a diagnosis other than ACS with a positive troponin assay (Chi^2=8.9, p<0.01). Unstable angina was diagnosed in 197 (76.9%) patients with an ACS diagnosis. Unstable angina represents 82.8% (197 patients out 238) of all NSTE-ACS patients. Eighteen patients with STEMI underwent troponin T testing, 5 had a negative troponin T result. Significantly more patients were discharged following a negative troponin assay result versus a positive result (Chi^2=27.9, p<0.001), whilst significantly more patients were referred following a positive result (Chi^2=57.7, p<0.001). Admission to a ward and mortality showed no statistical difference irrespective of the troponin result (p=0.54 and p=0.06 respectively).

Table 1 describes the number and proportion of comorbidities for the study population and Table 2 describes the odds ratios from the univariate logistic regression analysis.

Table 1: *Summary records of risk factors among study participants. Proportions are a function of all cases included in the sample (n=929).*

Risk factor	**Risk factor documented as present, n (%)**	**Risk factor not documented, n (%)**
Hypercholesterolaemia	346 (37.2)	452 (48.7)
Hypertension	709 (76.3)	2 (0.2)
Diabetes mellitus	365 (39.3)	5 (0.5)
Smoking	401 (43.2)	270 (29.0)
Family history	62 (6.7)	859 (92.4)
Obesity	75 (8.1)	844 (90.8)

Table 2: *Logistic regression to evaluate association of a positive troponin T assay and the risk factor variables with an ACS diagnosis*

Variable	**Odds ratio (OR)**	**95% Confidence interval**	**p-value**
Troponin T positive	4.24	2.73 - 6.57	<0.001
Hypercholesterolaemia	1.92	1.63 - 2.26	<0.001
Hypertension	1.92	1.32 - 2.78	<0.001
Smoking	1.25	1.05 - 1.49	0.01

Diabetes mellitus	1.11	0.83 - 1.48	0.47

Discussion

Even though ACS was significantly associated with a positive troponin assay result, there was undoubtedly a substantial number of patients diagnosed with ACS that had negative troponin T results; in other words, unstable angina (197 out of 256 patients; 76.9%). This proportion was substantially higher than the 5 - 10% Lim et al. described (21, 22). Critical assessment of the final diagnosis among ACS also showed that unstable angina represented 82.8% of all NSTE-ACS patients. Intuitively, the reliance to clinical and ECG findings may explain the high proportion of unstable angina. The troponin T assay at study site was seemingly a weak help in discriminating between the different types of NSTE-ACS. Indeed, newer, more and more sensitive troponin tests are expected to reduce the proportion of unstable angina to the benefice of NSTEMI. Admittedly, the present study is not designed to assess the validity of the troponin T assay at the study site, but the proportion of unstable angina is an eye-opener not easily to be ignored. With an unfavourable cardiac adverse events outlook, NSTEMI has far reaching implications compared to unstable angina and has to be diagnosed on time (18). Ultimately, it is important to thwart the overuse of the diagnosis unstable angina.

From an EC perspective, the value of a troponin test also lies in its ability to rule-out disease as the vast majority of patients presenting with a suspected diagnosis of ACS turn out not to have the disease. However, the findings of this study suggest the contrary with a sizable proportion of troponin negative patients diagnosed as NSTE-ACS and admitted. Clearly, clinical vigilance may have informed admissions as similar admission trends were observed regardless of the troponin T test results. What is concerning is that local clinicians' interpretations of troponin results are likely based on, and influenced by current international reference standards. Another disadvantage of the troponin T assay at the study site is its inability to calculate the delta value from indeterminate values as recommended (14, 19). Hypothetically, patients that are diagnosed as non-ACS on the basis of a flawed negative troponin result may come to harm. Likewise, over-diagnosis of ACS due to compensation for a flawed troponin assay will also be associated with an increased risk of harm (e.g. anticoagulation, missed alternative diagnosis, etc.).

Given the significant associations with a number of reported risk factors, it is likely that an ACS diagnosis significantly relied on clinical acumen and an interpretation of the history in addition to troponin findings. The current study did not evaluate for the ECG patterns commonly associated with ACS due to restricted study resources, a design limitation, but rather relied on the exit diagnosis which usually involved a specialist physician or emergency physician. Regarding risk factors, the

findings of this study join the INTERHEART study as they show an association of ACS to a number of known risk factors. It was interesting to note that diabetes was equally common among ACS and non-ACS patients. Conversely, it is disappointing that documentation of some risk factors, i.e. family history of cardiovascular events and obesity, was found to be poor. This is particularly important given that clinicians were seemingly applying more weight to the clinical examination and ECG findings during the ACS work-up.

Overall, ACS was found in about a quarter (256 out of 929 patients) of the study population. However, this doesn't necessarily represent the prevalence of ACS at Mitchells Plain hospital. Indeed many patients with STEMI would be treated promptly without requesting a troponin T test. Surprisingly, a few patients with STEMI (18 patients) had a troponin T testing in our study population. In these cases, prompt management of STEMI ensued regardless of troponin T results that were available only later. Some of these STEMI had a negative troponin T result. Without an in-depth analysis, particularly the inclusion of findings at the referral academic cardiology unit, negative troponin T STEMI may have most likely reflected the result of a too early test and/or a less sensitive assay. Another less likely reason may have been a misdiagnosis. However, requesting a troponin T test for an obvious STEMI (by ECG and clinical presentation) is not cost effective. Also, in the study population, usage of hospital services was higher among ACS patients as they were more likely to be admitted or referred to the academic hospital compared to non-ACS.

Although the study findings were anticipated, the extent of the findings were unexpected. The findings opened up questions about the limitations of the diagnostic process within the study setting, the validity of the test used and how these findings will impact on local ACS care. As a retrospective study, it relied heavily on the quality of data collected from patient files. The troponin interpretation protocol also has limitations, specifically with regards to serial investigations surrounding the result provided as a range. Other limitations of this study are: non-randomisation of the study sample and non-reporting of the 30-day major adverse cardiovascular events as well as the association of ECG findings. However, this study is one of the very first studies describing ACS in this lower-middle income population. Randomisation should certainly be considered in future studies. Including the ECG evaluation in the study protocol would have added an additional dimension to the evaluation of the NSTE-ACS diagnosis, but this would have had to be done independently to be of value. The study team did not have the resources to include ECG evaluation and therefore made use of the exit diagnosis to define whether ACS existed or not. Future studies should certainly consider independent interpretation of ECGs. This would improve scrutiny of the clinical diagnosis and thus provide a deeper understanding of how an ACS diagnosis is made in the local setting.

Considering the findings of this study and its limitations, further studies may be recommended to address the following issues: the contribution of the ECG findings to the diagnosis of ACS, the 30-day

major adverse cardiac events associated to ACS, the validity of the troponin T assay used in this study and the underlying diagnoses among non-ACS patients.

Conclusion

Despite internationally accepted reference standards, some facilities operating in LMICs continue to make use of troponin assays that are unable to reliably detect troponin rises. Emergency care clinicians working in LMICs are reminded of the value of a thorough history and physical examination when ACS is suspected; that a negative troponin should be considered truly negative only after close evaluation of a patient's symptoms, the history and ECG findings; and that serial troponin testing is not necessarily a panacea. The latter result should always be interpreted with due caution especially when presented with a range instead of an absolute value. Evaluation of the diagnostic process in the study setting, particularly focusing on the contribution of ECG findings, should be considered for future research. Wider ACS research in the region, particular with regards to the EC, should be encouraged in order to strengthen a case for better diagnostic tools for LMIC patients.

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PART C: ADDENDA

PART C: ADDENDA

Guidance for authors (South African Medical Journal)

Detailed author guidance is provided at the following link:

http://www.samj.org.za/index.php/samj/about/submissions

Research protocol

(as approved by the Human Research Ethics Committee- Stellenbosch University)

A descriptive study of the definitive diagnosis and outcome of patients tested for suspected acute coronary syndrome with the troponin T test at Mitchells Plain Hospital emergency centre

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A descriptive study of the definitive diagnosis and outcome of patients tested for suspected acute coronary syndrome with the troponin T test at Mitchells Plain Hospital emergency centre

I- PURPOSE OF THE STUDY

This study aims to review the current clinical and demographic data as well as the final diagnosis and disposition outcome of patients tested for suspected acute coronary syndrome (ACS) with the troponin T test presenting to Mitchells Plain Hospital Emergency Centre (EC). This descriptive study is primarily projected to inform the establishment of an ACS registry at Mitchells Plain Hospital EC. Ultimately, this knowledge will contribute to increase local awareness about ACS presentations to the EC among clinicians.

II- BACKGROUND

1- INTRODUCTION

The global burden of disease is shifting from communicable to non-communicable diseases (1). By 2020, among the non-communicable diseases, cardiovascular diseases and stroke will be the commonest causes of death and disability. The annual global death due to cardiovascular diseases will reach 24 million people by 2030 without intervention (1). Currently, more than 80% of cardiovascular related deaths occur in low-to-middle-income countries (1). ACS is the commonest cause of death and disability among patients with cardiovascular diseases (2). It basically comprises two entities: ST-elevated myocardial infarction and non-ST-elevated ACS (3, 4).

Current epidemiological knowledge about ACS relates mainly to high-income countries. There are only a few studies involving low-to-middle-income countries also revealing the increasing burden of cardiovascular diseases there (5). The INTERHEART study showed that the risk factors for cardiovascular disease remain similar worldwide (5). The major risk factors of cardiovascular diseases are: raised blood pressure, raised cholesterol levels, cigarette smoking, diabetes mellitus, physical activity and high fat diet (5).

Approach to ACS diagnosis, besides the examination and the electrocardiogram, involves the use of highly specific cardiac troponins for the diagnosis and risk stratification of ACS (5, 6). Assays use monoclonal antibodies to specifically detect either the cardiac troponin T or I (6-8). Rising troponin T levels are more specifically linked to cardiac necrosis (8). However, elevated troponin T levels may also be found in non-ACS conditions like heart failure, cardiomypathies, myocarditis, renal failure,

tachyarrhythmias, pulmonary embolism, strenuous exercises (7, 8). In the United States of America (USA), 6 million people are investigated annually for suspected ACS (9). Approximately a tenth of these patients are hospitalised with actual diagnosis of ACS (9). Also in the USA, patients with ACS have a median age of 68, in contrast to patients with ACS in low-to-middle-income countries who tend to be younger along thus affecting economic productivity (2, 4).

Furthermore the tenacity of burden of infectious diseases, coupled with the acceleration of non-communicable diseases, specifically in Sub-Saharan Africa, has led to a substantial burden of disease (9). Anecdotally a lot of research focuses on infectious disease, with less focus on non-communicable diseases such as ACS. Understanding local trends in presentation, testing and outcomes of patients presenting with suspected ACS will aid local policies and ultimately improve the acute care involved in managing ACS.

2- RESEARCH QUESTION

Among patients tested for suspected acute coronary syndrome with the troponin T test at Mitchells Plain Hospital EC, what were the final diagnoses and disposition (discharge from EC, inpatient stay, transfer and death)?

3- OBJECTIVES

For the purposes of the objectives, disposition outcome refers to the following variables:

- survival to discharge from EC,
- survival to discharge from Mitchells Plain hospital ward,
- survival to transfer and
- death during admission at Mitchells Plain hospital.

The objectives of this study are:

a. To compare the Troponin T results (positive/negative) to the disposition diagnosis (ACS/not ACS).

b. To compare the Troponin T results (positive/negative) to the disposition outcome.

c. Sub-objectives are:

   - To compare the disposition diagnosis (ACS/not ACS) to the disposition outcome

- To compare the Troponin T results (positive/negative) to risk factors (hypercholesterolemia, hypertension, diabetes mellitus, smoking, positive family history and obesity) documented during admission.
- To compare the disposition diagnosis (ACS/not ACS) to risk factors (hypercholesterolemia, hypertension, diabetes mellitus, smoking, positive family history and obesity) documented during admission.

III- METHODOLOGY

1- STUDY DESIGN

This design will be a descriptive, retrospective, cross-sectional study.

2- CHARACTERISTICS OF THE STUDY POPULATION AND AREA

The study population will be drawn from patients presenting to the Mitchells Plain Hospital EC; these patients mainly resides in the Mitchells Plain and surrounding suburbs of Cape Town (10). According to the 2011 Census, 310485 people lived in Mitchells Plain. Among those, 91% are of mixed ancestry, 7% are Black African, and the rest Asians and Whites (10). The 25 to 64 years old age group predominates and represents 50% of the population (10). Unemployment stands at 24% (10). The prevalence of ACS is not known in these areas, though it is perceived to be high.

Mitchells Plain Hospital EC has four adult beds in the adult resuscitation area. There is a paediatric resuscitation bed in a paediatric emergency suite. There are 13 adult beds in the trolley area, 9 chairs in the nebulisation room and a large number of chairs for the adult and paediatric minor ailment areas. Currently, Mitchells Plain Hospital EC is estimated to see 3600 to 3800 patients per month. The exact proportion of ACS patients from the overall cohort is not known but is also perceived to be high. Local treatment at Mitchells Plain Hospital EC tends to be the norm for ACS; patients are managed through the internal medicine department once diagnosed and admitted from the EC. Access to cardiology services, including angiography, is through Groote Schuur Hospital. The latter is not a primary service as far as ACS is concerned.

3- RECRUITMENT AND ENROLMENT

Study participants will be identified through the National Health Laboratory Services (NHLS) by searching for patients who have had troponin T testing performed at the Mitchells Plain Hospital EC during the period 1st July to 31st December 2015. A sample size of 384 consecutive subjects meeting the inclusion criteria (see below) will be

collected. The sample size calculation assumed a 50% proportion of positive clinical diagnosis (with α=0.05 and β=0.8). Given the retrospective nature of the data collection and bearing in mind that electronic record will be used to gather data (approximately 90% capture), it is possible (though not expected) that the study period may have to be extended to achieve this sample. This will be done by extending the study period until the required sample size has been achieved. The following patients that have had a troponin T testing performed for suspected ACS will be excluded from the study: subjects with missing electronic records and those with lacking demographic information (age and gender), the final diagnosis and/or outcome disposition. It is accepted that risk factors may be variably reported. This is further discussed in the limitations section and is the reason risk factors are only included as sub-objectives.

4- RESEARCH PROCEDURES AND DATA COLLECTION METHODS

Research process is visually described in **Figure 1**. All the study subjects will be identified through NHLS records and selected as consecutive troponin T tests over the study period. The hospital numbers associated with the NHLS outputs will then be used to access further variables (**Table 1**) through the electronic record. All patients' notes are captured electronically and stored in the electronic records.

If multiple troponin T tests have been performed during a single admission, only the troponin T test performed 12 hours post symptoms onset will be used for negative results or any positive results within 6 to 12 hours of symptoms onset. For the purpose of this study the troponin T result will be dichotomised. The troponin T test result is positive if the level is above 100 and negative if the level is below 50. For troponin T test values between 50 and 100, trends and clinical presentations are used to determine the final diagnosis. Where the symptoms onset is not stated, the time of presentation to Mitchells Plain Hospital EC will be assumed as the beginning of symptoms.

A sample size check will be performed after the selection of subjects with troponin T testing during the study period and the addition of relevant demographic and clinical data described in recruitment and enrolment above. The sample will then be anonymised by substituting the folder numbers with a unique study number. This will be done prior to data analysis starting.

5- DATA SAFETY AND MONITORING

Data form NHLS and electronic record will be captured in a Microsoft Excel spreadsheet. Names, addresses and other personal identifiable information other than the folder number will not be collected. Folder numbers will be replaced with study numbers once the database has been established and cleaned as described above. Only after

anonymising of the database has been completed will analysis start. Data will be kept in a password protected file on an access controlled, password protected office computer.

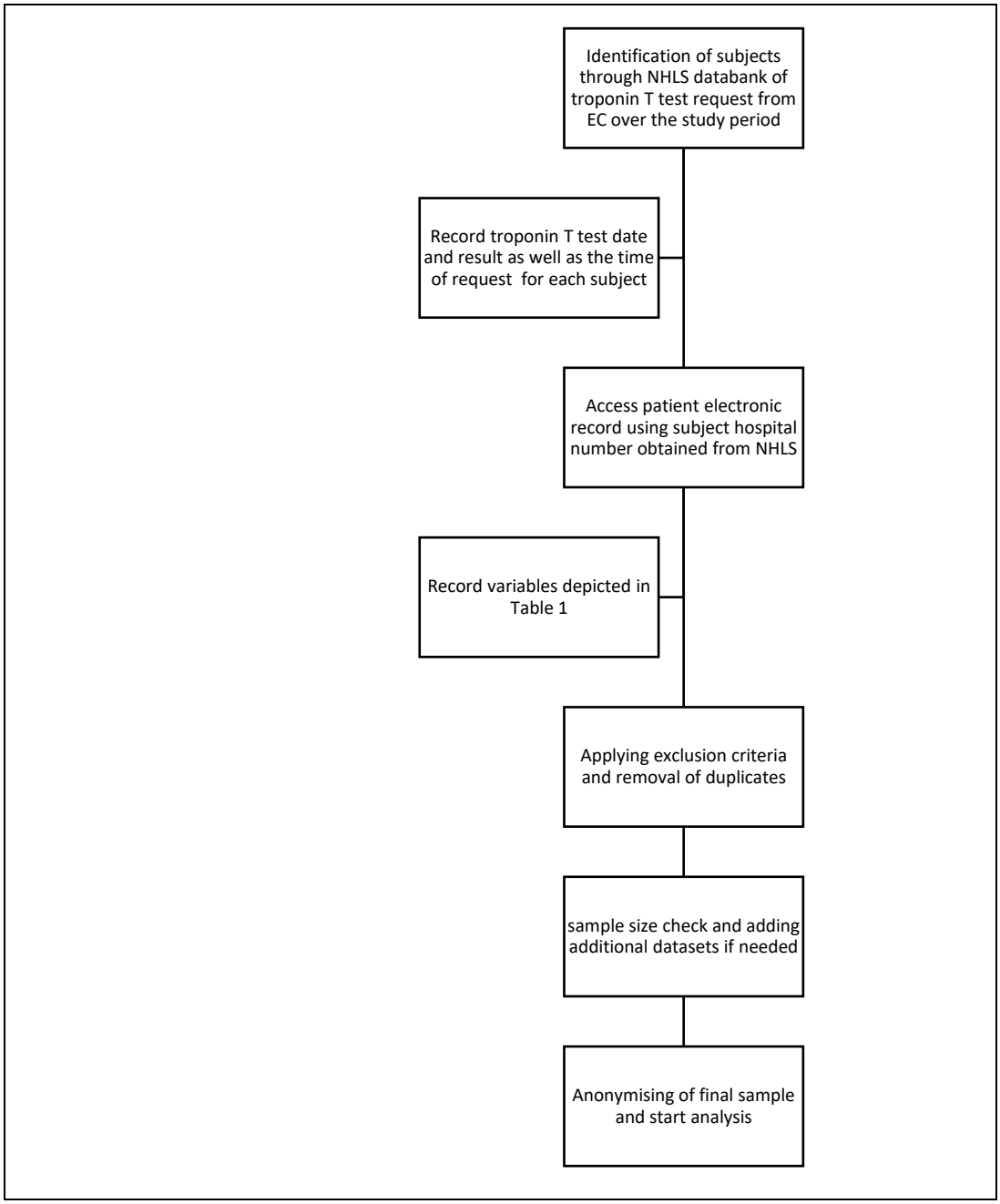

Figure 1: Research procedure and data collection

Table 1 Variables to be included in the data collection

- Folder number
- Age
- Gender
- Date and time of symptom onset
- Date and time of presentation to MPH EC
- Date and time of troponin request
- Troponin T result
- Diagnosis (ACS/ not ACS)
- Risk factors (hypercholesterolemia, hypertension, diabetes mellitus, smoking, positive family history and obesity)
- Date and time of disposition from MPH EC
- Disposition outcome:
    - Survival to discharge from EC,
    - Survival to discharge from Mitchells Plain hospital ward,
    - Survival to transfer and
    - Death during admission at Mitchells Plain hospital)

6- DATA ANALYSIS

Microsoft Excel and SPSS will be used for analysis. Numerical data (e.g. age) will be summarised as mean or median (central tendency) with standard deviation (SD) or interquartile range used to define spread. Categorical data (troponin T results, disposition, diagnosis at disposition and risk factors) will be expressed as frequencies. To compare troponin T results (positive/negative) to either the disposition (survival to discharge from EC, survival to discharge from Mitchells Plain hospital ward, survival to transfer and death during admission at Mitchells Plain hospital) or the disposition diagnosis (ACS/not ACS), relative risks of disposition or disposition diagnosis will be calculated and compared using the Chi^2-test. To compare the disposition diagnosis (ACS/not ACS) to ACS risk factors, and odds ratio of risk factors will be calculated and compared using the

Chi²-test. During Chi²-testing, a p value of less than 0.05 will be considered statistically significant. Ninety five percent confidence intervals will be presented where appropriate.

IV- ETHICAL CONSIDERATIONS

1- DESCRIPTION OF RISKS AND BENEFITS

The findings of this study are expected to raise the awareness and to improve ACS identification and management within the resource limited settings on the Cape Flats, specifically Mitchells Plain. Furthermore, its findings will contribute to the feasibility of establishing an ACS registry for the Mitchells Plain Hospital drainage area and, ultimately, the broader Western Cape Province. Conversely, particularly if a considerable number of troponin T testing results are negative, foreseen risks of misinterpretation may lead to reduce troponin T testing requests for cost-effectiveness.

2- INFORMED CONSENT PROCESS

Given the retrospective nature, data collection and analysis plan of the study a request will be made for a waiver of consent. Permission to pursue research will be obtained from the Human Research Ethics Committee of the University of Stellenbosch as well as Mitchells Plain Hospital through the Western Cape Provincial Government Department of Health/ National Health Research Database.

3- PRIVACY AND CONFIDENTIALITY

Data will be kept in a password protected file on an access controlled, password protected computer. The data will not include subjects' identities, e.g. names and national identity numbers. Folder numbers will be replaced with study numbers once the database has been established and cleaned as described above (data safety). Only after anonymising of the database will analysis start.

4- REIMBURSEMENT FOR PARTICIPATION

The data collection in this study does not involve any direct contact with study subjects. No re-imbursement will be required.

5- EMERGENCY CARE AND INSURANCE FOR RESEARCH-RELATED INJURIES

This study is retrospective and does not require any intervention on study subjects. No research-related injuries are expected to occur.

V- LIMITATIONS

The following limitations may be forseen:

- Reliance on the quality of pre-recorded data in a retrospective study, particularly the recording of ACS risk factors.
- Conclusions will reflect findings related to a specific area and may not be generalised.

VI- DISSEMINATION OF FINDINGS PLAN

The findings of the study will be assimilated and published in a medical peer review journal. Mitchells Plain Hospital will receive a copy of the dissertation to inform its management of the outcome of the study

VII- PROJECT TIMELINE

Table 2: Project timeline

	Oct 15	Nov 15	Dec 15	Jan 16	Feb 16	Mar 16	Apr 16	May 16	Jun 16	Jul 16	Aug 16	Sep 16	Oct 16	Nov 16	Dec 16	Jan 17	Feb 17	Mar 17	Apr 17
EMDRC Protocol		X	X																
Ethics				X	X	X													
National Health Database						X	X	X											
Data collection								X	X	X									
Data analysis										X	X	X	X	X					
Transcri														X	X	X	X	X	

bing final report																			
Submission																			X

VIII- RESOURCES UTILISATION

The following resources will be required to gather information and finalise the present study: NHLS database, electronic record, transportation and a computer. The NHLS database and the electronic record will be accessed using the Mitchells Plain Hospital computer system. Preliminarily, Mitchells Plain Hospital has verbally agreed to allow the use of its database and computer. Final agreement will be given after official application.

IX- BUDGET

Budget in Table 3 will be covered by own funds.

Table 3: Study budget

ITEMS	AMOUNT
Transportation	R 1000
Language editor	R 100
Statistician fee	R 500
Stationary	R 500
TOTAL	R 2100

X- REFERENCES

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Human Research and Ethics Committee approval

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Ethics Letter

08-Jun-2016

Ethics Reference #: S16/02/029
Title: A descriptive study of the definitive diagnosis and outcome of patients tested for suspected acute coronary syndrome with the troponin T test at Mitchells Plain Hospital emergency centre

Dear Dr Diulu Kabongo,

Your letter dated 2 June 2016 refers.

We acknowledge your response to stipulations and confirm that it is in order.

You may proceed with the research project.

If you have any queries or need further help, please contact the REC Office .

Sincerely,

REC Coordinator

Health Research Ethics Committee 2